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Injury and Disease Linkages

Effects of traumatic brain injury and posttraumatic stress disorder on Alzheimer's disease in veterans, using the Alzheimer's Disease Neuroimaging Initiative☆

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Abstract Both traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) are common problems resulting from military service, and both have been associated with increased risk of cognitive decline and dementia resulting from Alzheimer's disease (AD) or other causes. This study aims to use imaging techniques and biomarker analysis to determine whether traumatic brain injury (TBI) and/or PTSD resulting from combat or other traumas increase the risk for AD and decrease cognitive reserve in Veteran subjects, after accounting for age. Using military and Department of Veterans Affairs records, 65 Vietnam War veterans with a history of moderate or severe TBI with or without PTSD, 65 with ongoing PTSD without TBI, and 65 control subjects are being enrolled in this study at 19 sites. The study aims to select subject groups that are comparable in age, gender, ethnicity, and education. Subjects with mild cognitive impairment (MCI) or dementia are being excluded. However, a new study just beginning, and similar in size, will study subjects with TBI, subjects with PTSD, and control subjects with MCI. Baseline measurements of cognition, function, blood, and cerebrospinal fluid biomarkers; magnetic resonance images (structural, diffusion tensor, and resting state blood-level oxygen dependent (BOLD) functional magnetic resonance imaging); and amyloid positron emission tomographic (PET) images with florbetapir are being obtained. One-year follow-up measurements will be collected for most of the baseline procedures, with the exception of the lumbar puncture, the PET imaging, and apolipoprotein E genotyping. To date, 19 subjects with TBI only, 46 with PTSD only, and 15 with TBI and PTSD have been recruited and referred to 13 clinics to undergo the study protocol. It is expected that cohorts will be fully recruited by October 2014. This study is a first step toward the design and statistical powering of an AD prevention trial using at-risk veterans as subjects, and provides the basis for a larger, more comprehensive study of dementia risk factors in veterans.

Keywords: Traumatic brain injury; Posttraumatic stress disorder; Alzheimer's disease; Veterans; Neuroimaging

1. Introduction

Post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI) are well-documented risk factors for Alzheimer's disease (AD) [1–3]. AD is characterized by brain pathology consisting of extracellular plaques containing amyloid-β (Aβ), tangles of phosphorylated tau protein inside neurons, synapse loss, and neuronal loss, leading to dementia. Imaging studies using magnetic resonance imaging (MRI) and positron emission tomography (PET), and analysis of proteins in cerebrospinal fluid (CSF) have revealed that AD is associated with low concentrations of CSF Aβ and elevated tau or, equivalently, the high uptake of an Aβ [4] imaging agent such as [^{11}C] Pittsburgh compound B, or the more recently developed [^{18}F]-labeled amyloid PET ligands, such as florbetapir. Volumetric MRI has identified reduced volume of the entorhinal cortex, and hippocampus, and cortical thinning of the temporal and parietal cortices as being characteristic of AD [5].

TBI is defined as traumatically induced physiological disruption of brain function, as manifested by loss of consciousness, memory impairment, alteration of mental state, and/or focal neurological deficits. Diffuse injuries include hypoxia/ischemia, vascular damage, and diffuse macro-/microstructural axonal injury. Numerous epidemiologic studies have linked TBI to AD (reviewed in [6–12]). A history of TBI may be associated with earlier onset of AD [1,6,7,13–16] and the apolipoprotein E ε4 (*APOE* ε4) allele may worsen outcome [13,17–28]. Aβ plaques and intra-axonal Aβ deposits were found in approximately one-third of TBI subjects who died sometime after the TBI insult [29–36]. A biopsy study of TBI survivors confirmed Aβ pathology [37,38], even in young subjects, suggesting that TBI is causal [31,35]. Repetitive mild TBI is associated with the development of chronic traumatic encephalopathy (CTE), a progressive tauopathy, and TAR DNA-binding protein 43 (TDP-43) proteinopathy that may also result in a late-life dementia [39]. CTE is distinguished from AD by the relative lack of Aβ-containing neuritic plaques and by atrophy of the medial temporal lobe, diencephalon, and mammillary bodies only in late stages of disease [39], but the link between the two conditions is not yet clear. One possibility is that TBI is associated with CTE, which manifest as a form of "reduced brain reserve." Other possible long-term consequences of TBI are the development of aging-related Parkinson's disease, which co-occurs commonly with AD, amyotrophic lateral sclerosis [40], and other neurodegenerative disorders that involve coincidental cerebrovascular disease pathology [41]. A systematic review of the literature supported an association between a history of head injury in males and future development of AD (summary odds ratio, 2.29; range, 1.47–3.58) [1]. PTSD is an anxiety disorder that develops in some individuals after exposure to traumatic stress [42]. PTSD symptoms include flashbacks or nightmares and avoidance of stimuli; and increased anger, arousal, and hypervigilance [43–45]. Although these symptoms abate, they can persist for years or even decades [44]. The overall lifetime prevalence of PTSD in U.S. combat veterans is estimated at 6% to 31% [46,47]. The neuropathology underlying PTSD, separate from that associated with TBI, is completely unknown [40].

PTSD engenders an approximate doubling of the risk for AD and dementia in veterans [2]. However mechanisms of brain volume loss, cognitive impairment, and increased risk for dementia in PTSD are not known and may include reduced "cognitive reserve" suggested by impaired verbal memory in PTSD [48,49]; brain alterations in the hippocampus [50–54], anterior cingulate [52], and prefrontal structures (reviewed in [55]); or the association of PTSD with independent risk factors for dementia such as smoking, hypertension, hyperlipidemia, diabetes, obesity, inflammation, and major depression [56–58]. No study has examined whether PTSD is associated with increased deposition of AD-like tau or Aβ pathologies, Parkinson's disease-like Lewy bodies formed by α synuclein amyloid fibrils, or TDP-43 inclusions that are signatures of frontotemporal lobar degeneration and amyotrophic lateral sclerosis.

2. Aims and scope of the study

This study aims to investigate the associations between a history of TBI and/or current PTSD and brain AD pathology using methodology, infrastructure, and data collection techniques currently in use in the Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI [59–61] is a large public–private partnership that aims primarily to validate imaging and biomarkers for AD clinical trials. Standardized longitudinal, clinical, and cognitive [62,63] MRI [64]; fluorodeoxyglucose–PET and Pittsburgh compound B–PET [65]; blood and CSF biomarkers [66]; and genetics measurements [67,68] have been made on more than 800 participants. In 2010, funded by the federal stimulus package, the ADNI study moved into the "ADNI GO" phase. The ADNI GO research effort is the first of its kind to focus on participants who exhibit the earliest signs of memory loss in mild cognitive impairment (MCI)—both thought to be precursors to AD. The ADNI2 phase of the study commenced in 2011 and is modeled after the original ADNI study. ADNI2 uses clinical/cognitive tests, lumbar puncture for the collection of CSF, 3-T MRI, florbetapir amyloid PET scans, and fluorodeoxyglucose PET scans [69–72], and has enrolled a large cohort of new healthy control volunteers and subjects with early MCI, late MCI, and AD; and a new group consisting of those with subjective memory complaints. Across these three phases, more than 1600 unique participants have been enrolled. Subjects are seen at 59 sites throughout the United States and Canada.

For this study, we are enrolling three additional groups from military and veterans' records: (1) veterans with past history of TBI with or without PTSD, (2) veterans with ongoing PTSD without TBI, and (3) veteran control subjects comparable in age, gender, education, socioeconomic status to groups 1 and 2 who have no MCI or dementia. An attempt will also be made to match ethnicity. To maximize the statistical power to detect the effects of a history of TBI or ongoing PTSD on cognition, subjects with MCI will be excluded, because evidence of AD pathology has been reported in 50% to 60% of these subjects [73–75], and this would increase the difficulty in detecting an effect of PTSD or TBI. Furthermore, several groups (Drs. C. Rowe and M. Mintun, pers. comm.) have found that the effects of the *APOE* ε4 allele and age on amyloid PET positivity are more significant in cognitively normal subjects compared with patients with MCI or AD. Therefore, we will study subjects with normal cognition who are expected to have an age-associated prevalence of brain AD pathology of 10% to 30% [76–78].

3. Study hypotheses and exploratory analyses

Using the three groups, we are testing the primary hypothesis that veterans with a history of moderate to severe TBI and/or PTSD have increased evidence for AD pathophysiological markers (greater uptake on florbetapir amyloid PET scans, lower CSF Aβ levels, greater CSF tau and phosphorylated tau (p-tau) levels, greater baseline and longitudinal medial temporal brain atrophy, reduced baseline cognitive function, and a greater rate of change of cognitive function, particularly in delayed recall) compared with control subjects. Other major hypotheses are (1) that TBI and/or PTSD reduce cognitive reserve, causing greater cognitive impairment after accounting for age, educational status, prewar cognitive function, brain amyloid load, or hippocampal volume; and (2) that there are significant correlations between severity of TBI and/or the severity of PTSD, and greater cognitive impairment. We are also seeking to replicate reports that TBI is associated with reduced microstructural integrity in brain white matter in specific brain regions [79–81] and that PTSD is associated with reduced hippocampal volume compared with control subjects [50–54].

In addition, we are investigating whether TBI and PTSD alter the patterns of amyloid distribution or brain atrophy among TBI, PTSD, and control subjects, and whether these differ from patterns of nonveteran subjects in ADNI. We are also studying the relationship between cortical areas with amyloid deposition and underlying white matter integrity to determine whether axonal injury resulting from TBI is associated with greater amyloid accumulation or with less amyloid accumulation resulting from disconnection and reduced brain activity. We expect that these exploratory analyses will have low statistical significance after correction for multiple comparisons, and that they will require future replication.

4. Methods

This entire study has been approved by the Committee on Human Research at the University of California at San Francisco, the San Francisco VA Medical Center Research and Development Committee, and the Department of Defense Human Research Protection Office. All patients provide informed consent before being enrolled in the study.

4.1. Research participant selection and exclusion criteria

Vietnam veterans aged 60 to 80 years with documented history of TBI with or without PTSD, with ongoing PTSD

but without TBI, and veteran control subjects matching in age, gender, and education are being identified from Veterans Affairs records. Inclusion criteria for subjects with TBI are a documented history of moderate–severe nonpenetrating TBI that may be related to military service during the Vietnam War or to another trauma, and either no evidence or some evidence of PTSD (Clinician Administered PTSD Scale [CAPS] [82] score, >30 points). A minimum CAPS score of 40 points and no history of head trauma are required for inclusion in the PTSD group. Control subjects have no documented or self-history report of TBI, and no CAPS score greater than 29 points. Individuals are excluded from the study for potentially confounding factors, including a history of psychotic or neurologic illnesses, a recent history of alcohol or substance abuse, the presence of metal implants or claustrophobia that would prevent subjects undergoing MRI testing, and contraindications for lumbar puncture PET scan, or other procedures in this study.

4.2. Telephone screening and self-report assessments

Veteran volunteers within 150 miles of approved Department of Defense (DOD) ADNI sites are contacted initially by letter or by phone. Consenting volunteers undergo a telephone prescreen interview to document any history of TBI, including military-associated injury and all other traumas. Volunteers are questioned about their use of drugs and alcohol, medical history, current use of medications, and memory. The purpose of the prescreen interview is to rule out volunteers with exclusionary criteria, such as possible MCI or dementia (based on the Telephone Interview Cognitive Status assessment), inability to undergo MRI as a result of claustrophobia, or the presence of metal in the body, and other health issues that would make it unsafe for them to participate. Volunteers who pass the prescreen interview and who have given documented consent are then assessed using CAPS [82], which identifies PTSD and other exclusionary factors, such as psychotic illnesses (using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, nonpatient edition [83]; the Life Stressor Checklist, Revised; and the Addiction Severity Index Lite [84,85]). The following self-report measures are mailed to subjects and collected at the time of neurocognitive testing at the DOD ADNI sites: the Symptom Check-List-90-Revised [86], the Pittsburgh Sleep Quality Index [87], smoking status [88], number of pack years [89], the Short Form-12 Health Survey [90], and the Combat Exposure Scale [91].

After the Clinical telephone interview, eligible volunteers are referred to DOD ADNI sites for neurocognitive and clinical testing and imaging studies at baseline and at a 1-year follow-up.

4.3. Neurocognitive testing

At DOD ADNI sites, all participants are given the ADNI battery of neuropsychological tests designed to take fullest advantage of the *APOE* genotype, amyloid, and AD trajectories of decline for study data interpretation, in addition to the Armed Forces Qualification Test, which is unique to the DOD ADNI study [92,93]. The battery consists of the Montreal Cognitive Assessment [94], everyday cognition [95], the Mini-Mental State Examination, the Alzheimer's Disease Assessment Scale–Cognitive 13 [96], the Logical Memory Test I and II (Delayed Paragraph Recall) [97], the Boston Naming Test [98], the Category Fluency Test [99], the Clock Drawing Test, the American National Adult Reading Test [100], the Auditory Verbal Learning Test [101], the Trail Making Test Parts A and B [102–104], the Clinical Dementia Rating [105], the Activities of Daily Living/Functional Assessment Questionnaire [106], the Neuropsychiatric Inventory [107], and the Geriatric Depression Scale [108]. Information is also obtained on education level, a proxy for socioeconomic status [109], and health and cognitive status, including the Armed Forces Qualification Test taken during basic training (if available) to determine whether cognitive status before combat is predictive of AD or PTSD.

4.4. Classification of subjects using CSF biomarkers

CSF is obtained at baseline using lumbar puncture and is analyzed with established ADNI methods [63]. Briefly, CSF samples will be assayed to measure levels of Aβ42, total tau (t-tau) and tau phosphorylated at threonine 181 (p-tau$_{181}$) using the validated Luminex xMAP multiplex immunoassay platform [4,110–112]. The established pathological AD "signature" of biomarkers consisting of predefined cutoff values of t-tau, p-tau$_{181}$, and Aβ42 levels that are predictive of AD [110,112] is being used in combination with the logistic regression of tau, Aβ, and *APOE* ε4 alleles model [111] to delineate subjects with probable AD.

4.5. Imaging studies

4.5.1. Florbetapir amyloid imaging

Amyloid PET images are acquired using the radiotracer florbetapir ([^{18}F]AV-45) [70–73], with a Hoffman phantom reference, at participating PET centers. Acquisition and analysis is identical to previously published methods used in ADNI [113].

4.5.2. Magnetic resonance imaging

Imaging is performed on qualified ADNI GE systems [113]. Briefly, the protocol consists of the following image sequences: (1) a three-dimensional, T1-weighted volumetric scan using the inversion recovery - spoiled gradient recalled echo sequence (GE product analog to MPRAGE) [113]; (2) fluid attenuated inversion recovery to detect quantitative measures of white matter hyperintensity burden, and for qualitative grading of lacunar infarctions and evidence of closed head injury; (3) T2* gradient echo to capture evidence of hemosiderin deposition, which could indicate remote cortical contusion, shearing injury, or prior subarachnoid hemorrhage; (4) diffusion tensor imaging, as previously

described in ADNI protocols [113], to detect traumatic shearing injury; and (5) resting-state task-free functional MRI consisting of 103 volumes at 3.3-mm^3 resolution with a duration of 7 minutes to investigate the role of the functional network in dementia. Three-dimensional T1-weighted volumetric images are analyzed using FreeSurfer software (Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA, USA) [114], and volume measurements of anatomic brain regions and geometric measures of cortical regions will be computed. Images will be analyzed using identical methods to ADNI.

4.6. Statistical analysis

Primary hypotheses will be tested statistically using uptake on florbetapir scans; CSF Aβ; t-tau and p-tau$_{181}$; volumes of the hippocampus, entorhinal cortex, and parietal/temporal cortices; diffusion tensor imaging summary measures; and measures of cognitive function as primary outcomes. Baseline levels and change (difference scores between month 12 and baseline assessments) will be compared among groups using analysis of variance. When the global F-test for group difference is significant, post hoc pairwise tests, adjusting for multiple comparisons using the Bonferroni or Tukey's Honestly Significant Difference approach, will be used to identify specific group differences. Linear regression models will be used to account for potential confounders, including the presence of an *APOE* ε4 allele. A priori power analyses for each class of primary hypotheses have been calculated using nQuery [115] assuming a two-sided test.

4.7. Informatics and data release

All data are deidentified and uploaded to the Alzheimer's Disease Cooperative Study database at the University of California San Diego, and all magnetic resonance images and PET scans are uploaded to the Laboratory of Neuroimaging database [116] to be available, like ADNI data, to all qualified scientists, without embargo.

5. Current study progress

The names and contact information of Vietnam veterans who are service connected for PTSD and/or TBI were identified from Veterans Affairs compensation and pension records and Veterans Affairs health records. An additional group of Vietnam veterans service connected for traumas not related to PTSD, head trauma, or dementia were selected for the control group.

All subjects are contacted initially by mail, with a telephone follow-up to complete a prescreen interview to assess eligibility for study enrollment. The mail effort includes a letter, brochure, and response postcard. Subjects can call the toll-free study number or return the postcard and participate in the prescreen interview or opt out. Study staff call veterans who express interest and those who have not responded. No calls are made to those who have opted out. Table 1 summarizes the current prescreen effort. To date, 8113 letters have been mailed to selected Vietnam veterans. The overall response to this initial mail effort has been positive, as 12.4% of subjects expressed a desire to participate, whereas 4.5% declined. Telephone calls have been made to 4372 subjects. Of those called, 765 have declined (17.5%). The main reasons for declining are "not interested" and/or "too much involved" (lumbar puncture, PET, MRI). About a third (31.0%) completed the prescreen interview. The exclusion rate of those that completed this screen is 73.0%. The main reasons for excluding a subject involve circumstances that make it unsafe for the subject to undergo an MRI, a PET scan, or a lumbar puncture, such as metal or shrapnel in the body, unstable medical conditions, or current use of certain medications. Those subjects who complete the screening questions and are found to be eligible are mailed a consent form. Currently, 366 subjects (27.0%) have been sent a consent form and additional health and medical questionnaires. Again, the response to the study has been positive; only 24.6% of subjects who received the consent form declined to participate, whereas 214 (58.5%) signed

Table 1
Summary of each phase of the recruitment effort

Mail effort	Call effort	Completed screens	Consents sent	Signed consents received	SCID CAPS referrals	Clinic referrals by cohort
8113	4372	1356	60	214	3	TBI only, 19 (20%); both, 15 (15.8%)
Brochures mailed	Subjects called	Subjects screened	Waiting 14.9%	Signed and received	Scheduled	TBI/both, 35.8%
1005	765	990	90	55	61	46
12.4%	17.5%	73.0%	24.6%	25.7%	39.1%	48.4%
Respond yes	Subjects decline	Subjects excluded	Subjects declined	Subjects excluded	Subjects failed	PTSD only
367	1356	366	214	159	95	15
4.5%	31.0%	27.0%	58.5%	74.3%	60.9%	15.8%
Respond no	Subjects screened	Consents mailed	Signed and received	Referred SCID CAPS	Passed to clinic	Control subjects

Abbreviations: SCID, Structured clinical interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; CAPS, Clinician-Administered PTSD Scale; TBI, traumatic brain injury; PTSD, posttraumatic stress disorder.

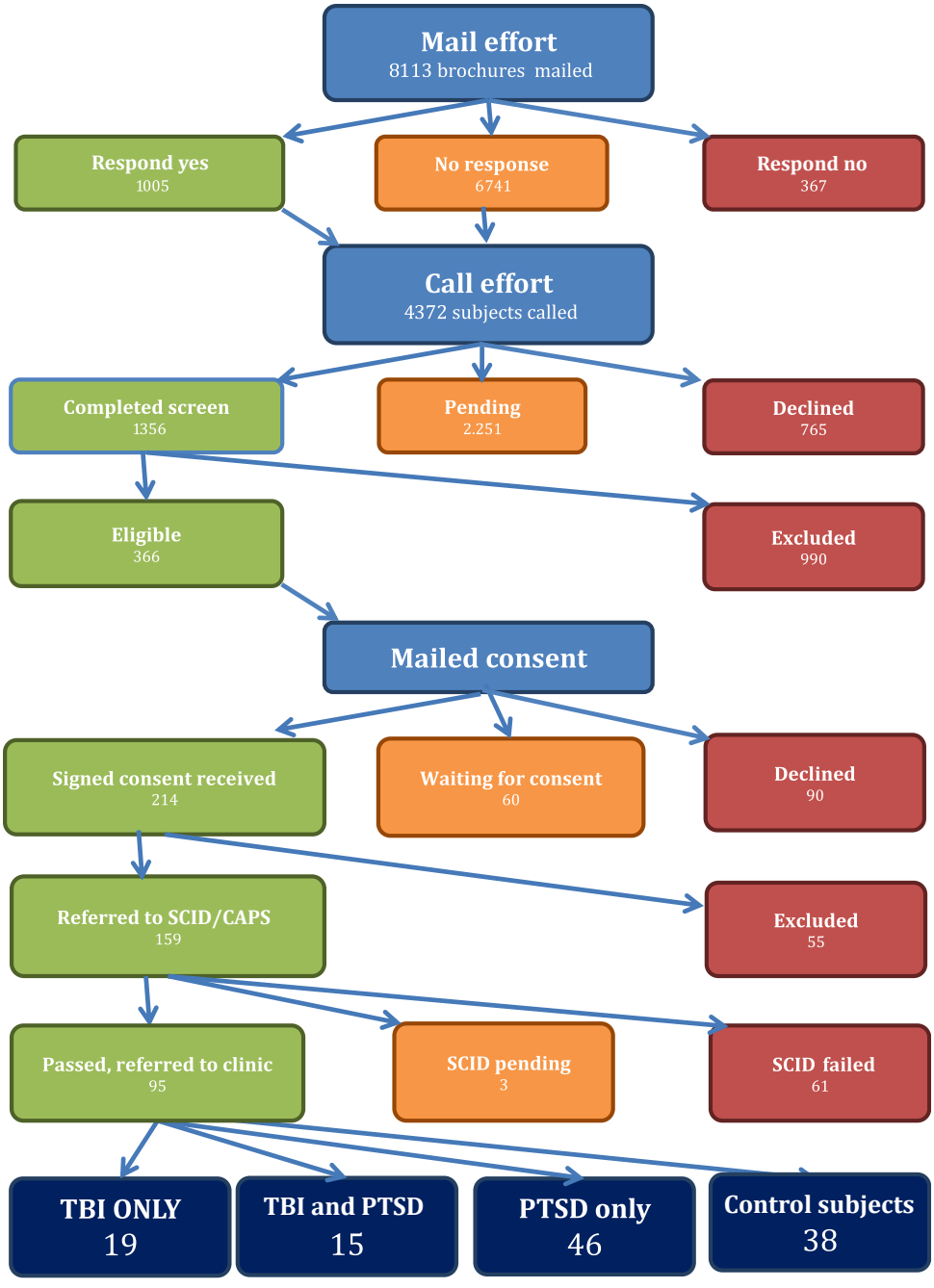

Fig. 1. Summary of each phase of the recruitment effort. SCID, Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; CAPS, Clinician-Administered PTSD Scale; TBI, traumatic brain injury; PTSD, posttraumatic stress disorder.

and returned the required forms. When received in the study office, the additional health forms are reviewed by staff to ensure subject safety. An additional 25.7% have been excluded at this stage as a result of the disclosure of other health issues not reported in the prescreen. Subjects who have given written consent to the study and who are assessed as safe to continue are next referred for a structured clinical interview (Structured clinical interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition CAPS); to date, 159 subjects (74.3%) of those who returned their signed forms have been referred to the clinical interview, which assesses the presence of PTSD, other psychological disorders, and drug and alcohol abuse. Currently, 39.1% of subjects were excluded after the clinical interview because they did not have current PTSD (for the PTSD cohort) or they disclosed an exclusionary criterion (e.g. drug and/or alcohol abuse, schizophrenia, bipolar disorder). Subjects who match one of the study cohorts and do not meet any exclusionary criteria are referred to the clinic for additional screening procedures (medical history, cognitive

testing, and a screening MRI); currently, 95 subjects (60.9%) referred to the clinical interview have also been referred to one of the study clinics: 46 (48.4%) of the total clinic referrals are in the PTSD-only cohort, 19 subjects (20.0%) are in the TBI-only cohort, 15 (15.8%) are in the combined cohort (TBI and some PTSD), and 15 (15.8%) are control subjects. Subjects who meet all inclusion criteria after completing the screening procedures at the clinic are formally enrolled in the study. As of November 4, 2013, 19 of 95 subjects referred to the clinics have completed the screening battery and have been enrolled. The screening and enrollment process and progress to date are summarized in Table 1 and Fig. 1.

6. Limitations of the study

One potential limitation of this study design is that TBI and PTSD may be associated with a much greater incidence of MCI and dementia, and by excluding such subjects from our study we may be biasing the sample. This limitation is now offset by the funding of an additional study of similar magnitude that is focusing on subjects with MCI. Another limitation is that it will not be possible to distinguish cognitive impairment and MCI resulting from AD pathology from cognitive impairment and MCI resulting from TBI or other factors by telephone interview.

7. Conclusions

In conclusion, this study is designed to provide sufficient power to detect the main effects of TBI and PTSD on AD pathology measured with imaging and biomarkers. The results of these studies may provide insight into the question of whether TBI and PTSD alter the pattern of cognitive impairments, amyloid distribution, or brain atrophy. The results of this study may provide insight into the question of whether or not TBI and PTSD alter the pattern of cognitive impairments, amyloid distribution or brain atrophy and may eventually lead to an AD prevention trial in veterans with risk factors for the development of AD.

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